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EXAMINER WOOLWINE, SAMUEL C				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/539,628

Applicant(s)

HINNAH, SILKE

Examiner

SAMUEL WOOLWINE

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 July 2008.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-40 is/are rejected.
7) ☒ Claim(s) 1-40 is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 17 June 2005 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-8508)
Paper No(s)/Mail Date 09/29/2005
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

Status

This application has been transferred to Examiner Samuel Woolwine, whose contact information appears below.

Applicant's election with traverse of claims 1-38 is acknowledged. The examiner agrees that claims 39 and 40 are not patentably distinct from the method of claim 1. Therefore the requirement for restriction as between claims 1-38 and 39-40 made in the Office action mailed 06/11/2008 is withdrawn.

Claim Objections

Claims 1 and 2 are objected to for the following informalities: the phrase "wherein...the solid support is labeled with a second reporter different from the first reporter, imaging the sample..." (last indented section of each claim) is grammatically incorrect. The limitation will be construed as "wherein...the solid support is labeled with a second reporter different from the first reporter, and the detection comprises imaging the sample...". Because claims 3-40 depend ultimately from either claim 1 or 2, they are objected to for the same reason. Appropriate correction is required.

Drawings

The drawings are objected to because figure 4 contains nucleic acid sequences not identified with sequence identifiers. 37 CFR 1.821(d) states:

"Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application."

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Interpretation

Independent claims 1 and 2 recite *detecting the detection probes*, *wherein...* followed by two indented sections connected by an "and/or". The two sections describe different alternatives for the detecting step (one where quenchers are used to quench signal from unbound probe, another where the solid support comprises a reporter used to generate a mask for detecting the detection probes/oligonucleotides). While it is recognized that the claims encompass an embodiment employing both alternatives, the "or" option necessitates an examination of two methods: one involving

only the quencher alternative, another involving only the masking alternative. Certain dependent claims recite limitations invoking one or the other of these alternatives. For example, claim 7, which recites "quenching oligonucleotides", invokes the quencher alternative. On the other hand, claim 4, which recites "wherein the first and/or second reporter..." invokes the masking alternative. There are no claims requiring that *both* the quenching *and* masking alternatives are performed. Any rejections made over the prior art will specify whether the rejection applies to the quenching or masking alternative, or both.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 6, 8, 10-15, 17, 18, 21-28, 30-33, 37 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a

question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance:

Claim 4 recites the broad recitation "luminescent", and the claim also recites "in particular fluorescent" which is the narrower statement of the range/limitation.

Claim 6 recites the broad recitation "the detection probes", and the claim also recites "in particular the detection oligonucleotides" which is the narrower statement of the range/limitation.

Claim 8 recites the broad recitation "at least 1°C...higher", and the claim also recites "more preferably at least 2°C, even more preferably at least 5°C and most preferably at least 10°C higher" which is the narrower statement of the range/limitation.

Claims 12 and 13 recite the broad recitation "the capture probes", and the claim also recites "in particular capture oligonucleotides" which is the narrower statement of the range/limitation.

Claims 14, 17, 21, 22, 24-26, 30-33, 37 and 38 recite either "capture probes/capture oligonucleotides", "detection probes/detection oligonucleotides", or "quenching probes/quenching oligonucleotides"; in all cases the recitation "oligonucleotides" is a narrower statement of the broader recitation "probes". Claims 15, 18 and 28 depend from claims 14, 17 and 26, respectively, and are therefore rejected for the same reason.

Claims 6, 12-14, 17, 21, 22, 24-26, 30-33, 37 and 38 recite the limitation "oligonucleotides" in reference to the "probes". There is insufficient antecedent basis for this limitation in the claim. These claims ultimately depend from claim 1, and claim 1 does not recite any oligonucleotides, but merely "probes". There is no intervening claim that further specifies that the "probes" are "oligonucleotides" (compare with claim 34, which *does* further specify "oligonucleotides"—however, none of the rejected claims depend from claim 34). Claims 15, 18, 23 and 28 depend from claims 14, 17, 22 and 26, respectively, and are therefore rejected for the same reason.

In cases where the claim recites "oligonucleotides" without proper antecedent basis, or where the claim recites the broader term "probes" followed by the narrower term "oligonucleotides" (except for the situation of a "wherein" clause as in claim 34), the examiner will construe the claim as simply reciting "probes".

Claim 38 also suffers from lack of antecedent basis for the recitation *the affinity units attached thereto* and *affinity units of the capture probes/capture oligonucleotides*. Claim 38 depends from claim 37, which depends from claim 21, which depends from claim 1. None of these claims recite any affinity units attached to solid supports or capture probes/oligonucleotides. For purposes of examination over the prior art, claim 38 will be construed in light of claim 14, which recites that the capture probes/oligonucleotides comprise a first affinity unit and a second affinity unit is attached to the solid support.

Claims 10 and 11 recite the limitations *wherein contacting the sample with the quenching oligonucleotides is performed under second hybridization conditions and wherein said second hybridization conditions do not destabilize a hybrid between detection oligonucleotides and analyte formed under said first conditions*, respectively. There is insufficient antecedent basis for these limitations in the claims. The claim dependency runs from claim 2 to claim 10 to claim 11, and none of these claims ever recited a "first hybridization condition". While it is recognized that claim 9 recites such a limitation, claim 9 is not in the line of dependency and thus the offending limitations are without antecedent basis. Appropriate correction is required.

Claim 27 suffers from lack of antecedent basis for the recitation *and the quenching unit is...* Claim 27 depends from claim 1, which recites *quenching probes* but does not recite a *quenching unit*. As Applicant has further limited claim 1 in claim 26 to specifically recite that the *quenching probes/oligonucleotides have a quenching unit*, Applicant has made a distinction between a "quenching probe" and a "quenching unit". However, as claim 26 is not in the line of dependency between claim 1 and claim 27, the recitation of *quenching unit* in claim 27 has no antecedent basis. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-6, 12-14, 16-18, 21, 29-37 and 40 are rejected under 35

U.S.C. 102(e) as being anticipated by Kelso (US 2003/0129296, filed July 17, 2002, priority date July 17, 2001).

This rejection applies to the "masking" alternative recited in claim 1. Kelso teaches a method of detecting target molecules using capture particles upon which capture agents are immobilized (paragraph [0006]). In one embodiment, the capture agent is an antibody and a labeled secondary antibody is used to label the target captured by the capture particle (paragraphs [0108]-[0109]).

With regard to claim 1, Kelso teaches *a method for detecting an analyte in a sample comprising the steps of providing detection probes being labeled with a first reporter,*

See paragraphs [0108]-[0109] where Kelso describes a one-step or two-step sandwich immunoassay wherein a labeled secondary antibody is used to bind a target. This labeled secondary antibody qualifies as a detection probe labeled with a first reporter.

which detection probes are capable of binding to the analyte,

See paragraphs [0108]-[0109]. It would have been understood by one of ordinary skill in the art from the cited passages that the purpose of the labeled secondary antibody was to bind the target in the test sample.

providing a solid support,

providing capture probes being bound or capable of binding to the solid support,

See paragraphs [0108]-[0109], where Kelso describes capture particles comprising attached antibody (paragraph [0108]):

"In some embodiments, one component of a detection assay (e.g. antibody or oligonucleotide) is attached to a particle and serves as the capture reagent. Other components of a detection assay (e.g., secondary antibody, nucleic acid cleavage enzymes, etc.) may then be added before, after, or simultaneously with a sample suspected of containing target molecules (i.e. a test sample)."

which capture probes are capable of binding to the analyte,

thus concentrating the analyte on the solid support,

It would have been understood by one of ordinary skill in the art from the cited passages that the purpose of the antibody attached to the capture particle was to bind the target in the test sample, thus concentrating the target on the particles.

contacting the sample with the detection probes, the solid support and the capture probes, and detecting the detection probes,

See paragraphs [0108]-[0109], e.g. at paragraph [0108]:

"In some embodiments, one component of a detection assay (e.g. antibody or oligonucleotide) is attached to a particle and serves as the capture reagent. Other

components of a detection assay (e.g., secondary antibody, nucleic acid cleavage enzymes, etc.) may then be added before, after, or simultaneously with a sample suspected of containing target molecules (i.e. a test sample)."

wherein the solid support is labeled with a second reporter different from the first reporter,

See paragraph [0124], where Kelso teaches the incorporation of a fluorescent dye into the capture particles to aid in focusing and provide a reference signal. It would have been understood by one of skill in the art that this would have required a "different" reporter than used for the detection probe (i.e. the labeled secondary antibody in the embodiment described in paragraphs [0108]-[0109]). If the label on the secondary antibody was the same as the reference fluor of the capture particles, how would one have distinguished whether the target was bound by the capture particle? In other words, if the label on the secondary antibody was the same as the reference fluor of the capture particles, the capture particles would have registered a positive signal regardless of the presence of target. See also paragraphs [0189]-[0191] and [0195]-[0208], where Kelso describes imaging the capture particles using "longer wavelength excitation light" (paragraph [0190]) to image the capture particles based on the reference fluor to create a mask, followed by imaging the capture particles to detect the target after "the filter block was switched to the target fluor channel" (paragraph [0191]). This implies that the reference fluor and the target fluor were not the same.

imaging the sample at an emission wavelength of the second reporter,

generating a mask obtained from imaging the sample at the emission wavelength of the second reporter

See paragraph [0190]:

"A full-field transmitted light or reference fluor image was then captured, typically with exposure times of 0.01 to 0.2 seconds. By focusing with low-intensity transmitted light or longer wavelength excitation light, photo-bleaching of the target labels was minimized. The transmitted light and reference fluor images were also used to generate masks for measuring target fluorescence levels (see below)."

and applying this mask to an image of the sample used for detecting the detection oligonucleotides

See paragraphs [0189]-[0191] and [0195]-[0208], where Kelso describes imaging the capture particles using "longer wavelength excitation light" (paragraph [0190]) to image the capture particles based on the reference fluor to create a mask, followed by imaging the capture particles to detect the target after "the filter block was switched to the target fluor channel" (paragraph [0191]). At paragraph [0196], Kelso states:

"Fluorescence intensities were measured with a binary mask generated from the transmitted light or reference fluor image."

With regard to claim 3, as there is no explicit definition of "homogeneous format" in the specification, the term does not distinguish over the method taught by Kelso.

With regard to claims 4 and 5, Kelso teaches the incorporation of a fluorescent dye into the capture particles to aid in focusing and provide a reference signal (paragraph [0124]). Hence, at least the "second reporter" is both fluorescent and a dye.

With regard to claim 6, see paragraphs [0189]-[0191] and [0195]-[0208], where Kelso describes imaging the capture particles using "longer wavelength excitation light" (paragraph [0190]) to image the capture particles based on the reference fluor to create a mask, followed by imaging the capture particles to detect the target after "the filter block was switched to the target fluor channel" (paragraph [0191]). Thus, in the embodiment taught in paragraphs [0108]-[0109] (i.e. a sandwich antibody format with a labeled secondary antibody), the image processing method taught in paragraphs [0189]-[0191] and [0195]-[0208] meets the limitations of claim 6. Note the term "dye" is not defined in the specification in such a way as to distinguish over the "target fluor" taught in paragraph [0191]. Also note that the phrase "in particular the detection oligonucleotides" is not considered required by the claim (see final statement of the rejection under 35 U.S.C. 112, 2nd paragraph above).

With regard to claim 12, Kelso teaches that the capture probes (which he refers to as "capture reagents") may be covalently attached to the solid support (which he refers to as "capture particles"; see paragraph [0031]). Also note that the phrase "in particular the capture oligonucleotides" is not considered required by the claim (see final statement of the rejection under 35 U.S.C. 112, 2nd paragraph above).

With regard to claims 13 and 14, Kelso teaches (paragraph [0070]) that "particles coated with protein A may be selected for preparation of an array of antibody probes". This represents an affinity interaction, as protein A binds to antibody through an affinity (not a covalent) interaction.

With regard to claim 16, the term "bead" does not structurally distinguish over the term "particle" as taught by Kelso in paragraph [0030]. Note also that Kelso teaches an exemplary particle which he characterizes with the term "bead" (paragraph [0072]: "latex beads").

With regard to claim 17, Kelso describes imaging the capture particles using "longer wavelength excitation light" (paragraph [0190]) to image the capture particles based on the reference fluor to create a mask, followed by imaging the capture particles to detect the target after "the filter block was switched to the target fluor channel" (paragraph [0191]). This implies that the reference fluor ("second reporter") and the target fluor ("first reporter") were subjected to different excitation wavelengths. Note that the limitation "detection oligonucleotides" is not considered required by the claim (see final statement of the rejection under 35 U.S.C. 112, 2nd paragraph above).

With regard to claim 18, see paragraph [0187] where Kelso describes the two filter sets used for imaging the reference fluor and the target fluor. One filter set was 480(excitation)/535(emission) and the other set was 545(excitation)/610(emission). In paragraph [0190] Kelso discusses using "longer wavelength excitation light" to create an image of the reference fluor (corresponding to the claimed "second reporter"). In paragraph [0191] Kelso discusses imaging the target fluor after "the filter block was switched to the target fluor channel". This implies the 480/535 filter set was used for the target fluor ("first reporter"), while the 545/610 filter set was used for the reference fluor ("second reporter"). As can be seen, excitation wavelengths 480 and 545 differ by at least 50 nm, as do emission wavelengths 535 and 610.

With regard to claim 21, Kelso teaches that arrays of different types of capture particles can be formed by attaching different species of capture reagents to different species of encoded particles (see paragraphs [0008] and [0072]; and see paragraph [0006] where "capture particles" are clearly indicated as comprising capture reagents attached to particles). Kelso teaches at paragraph [0055] that "capture particles are encoded such that many unique species of capture particles can be immobilized in the same spot (e.g. allowing the detection of multiple target molecules in a single capture-spot)", and at paragraph [0085]: "capture particle solutions are prepared by pooling subsets of distinctly labeled subpools of capture particles such that the capture particle solution contains many different populations (i.e. unique species) of capture particles. In this regard, multiplex analysis may be carried out." In the context of a sandwich immunoassay as described in paragraphs [0108]-[0109], these teachings imply using different species of capture particles, each species having a different antibody bound thereto (as a "capture probe") for binding different targets ("analytes"), thus meeting the *wherein at least two different analytes are detected by providing...at least two different sets of capture probes* limitations of claim 21. The cited passages also imply *providing at least two different sets of detection probe* (corresponding to the labeled secondary antibodies described in paragraphs [0108]-[0109]). Note that the limitations "capture oligonucleotides" and "detection oligonucleotides" are not considered required by the claim (see final statement of the rejection under 35 U.S.C. 112, 2nd paragraph above).

With regard to claims 29 and 30, Kelso teaches quantifying the analyte based on levels of attached labels (paragraph [0055], last sentence: "using an optical system,

capture particles are located, identified, and the levels of attached labels measured (e.g. the amount of bound target is determined)"). In the context of the embodiment of [0108]-[0109] (i.e. a sandwich antibody format with a labeled secondary antibody), the "levels of attached labels" corresponds to levels of attached labeled secondary antibody, i.e. the "detection probes". Note that the limitation "detection oligonucleotides" is not considered required by the claim (see final statement of the rejection under 35 U.S.C. 112, 2nd paragraph above).

With regard to claim 31, in the context of the embodiment of [0108]-[0109] (i.e. a sandwich antibody format with a labeled secondary antibody) and in the context of the imaging method discussed at paragraphs [0189]-[0191] and [0195]-[0208], it is clear that the amount of detection probe (labeled secondary antibody) would be expressed as an emission intensity (e.g. paragraph [0196]: "Fluorescence intensities were measured with a binary mask generated from the transmitted light or reference fluor image.>"). Note that the limitation "detection oligonucleotides" is not considered required by the claim (see final statement of the rejection under 35 U.S.C. 112, 2nd paragraph above).

With regard to claim 32, the phrase "determining an intensity of a background emission in the vicinity of the solid support" is relative in terms of how close to the solid support a region must be in order to be "in the vicinity of" the solid support. Therefore, the broadest reasonable interpretation of this phrase is "determining an intensity of a background emission of a region devoid of the solid support". Kelso teaches at paragraph [0208]: "Film background was measured on the original fluorescence image with the Show Region Statistics tool. A region devoid of particles was manually

selected." Kelso teaches at paragraph [0219]: "Net median particle fluorescence, MPF, was determined by subtracting the film background, FBF, from the median particle value." Hence, Kelso teaches determining a background emission in the vicinity of the solid support (particle) and considering such intensity when determining the amount of detection probes (in the context of the sandwich antibody assay taught at paragraphs [0108]-[0109], "detection probes" correspond to the labeled secondary antibody). Note that the limitation "detection oligonucleotides" is not considered required by the claim (see final statement of the rejection under 35 U.S.C. 112, 2nd paragraph above).

With regard to claim 33, Kelso describes imaging the capture particles using "longer wavelength excitation light" (paragraph [0190]) to image the capture particles based on the reference fluor to create a mask, followed by imaging the capture particles to detect the target after "the filter block was switched to the target fluor channel" (paragraph [0191]). In the context of the sandwich antibody assay taught at paragraphs [0108]-[0109], the "target fluor channel" would correspond to the emission wavelength of the label ("first reporter") on the labeled secondary antibody ("detection probe"). Note that the limitation "detection oligonucleotides" is not considered required by the claim (see final statement of the rejection under 35 U.S.C. 112, 2nd paragraph above).

With regard to claim 34, in the context of the sandwich antibody assay taught at paragraphs [0108]-[0109], "detection probes" correspond to the labeled secondary antibody.

With regard to claim 35, Kelso teaches at paragraph [0067]: "Preferably, the capture reagents are capable of binding target molecules, including, but not limited to,

an antibody (both monoclonal and polyclonal), a receptor, a hapten, an enzyme, a protein...". Hence, Kelso teaches the analyte (target) can be a protein.

With regard to claim 36, Kelso teaches test samples may include tissue homogenates and cell extracts (paragraph [0120]) which are not distinguishable from the claimed "cell lysate" or "crude cell lysate", and which certainly qualify as "in vitro prepared" samples, since homogenization and extraction are "in vitro" processes.

With regard to claim 37, Kelso teaches that arrays of different types of capture particles can be formed by attaching different species of capture reagents ("capture probes") to different species of encoded particles (see paragraphs [0008] and [0072]; and see paragraph [0006] where "capture particles" are clearly indicated as comprising capture reagents attached to particles). Note that the limitation "capture oligonucleotides" is not considered required by the claim (see final statement of the rejection under 35 U.S.C. 112, 2nd paragraph above).

With regard to claim 40, Kelso teaches the methods of his disclosure may be used in the detection of disease (paragraph [0068]), i.e. used in diagnostics.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kelso (US 2003/0129296, filed July 17, 2002, priority date July 17, 2001) in view of Oberhardt (US 6,251,615).

This rejection applies to the "masking" alternative recited in claim 1.

The teachings of Kelso have been discussed (see rejection of claims 1, 3-6, 12-14, 16-18, 21, 29-37 and 40 over Kelso under 35 U.S.C. 102(e) above).

With regard to claim 15, it is noted that Kelso does teach a "capture probe" in the form of an oligonucleotide comprising biotin and a solid support (particle) comprising avidin or streptavidin (see paragraph [0149]). Kelso also specifically teaches that the capture reagent attached to the capture particles can be oligonucleotides (paragraph [0006]). However, as Kelso teaches no embodiments where an oligonucleotide is used as a capture probe *in combination* with a second, labeled detection probe, the limitations of claim 1, and thus claim 15, are not met for the case of an oligonucleotide capture probe.

In addition, Kelso teaches the biotin/avidin or biotin/streptavidin binding pairs insofar as that biotin, avidin or streptavidin may *be* the capture probe (i.e. capture reagent) while one of the remaining members of the binding pair may *be* the target (paragraph [0068]).

In addition, Kelso teaches using biotin as a capture probe on a solid support (particle) to capture *either* an antibody that binds specifically to biotin (no involvement of avidin or streptavidin) *or* avidin labeled with R-phycoerythrin (paragraph [0229]).

The only embodiment taught by Kelso meeting the limitations of independent claim 1 with regard to detector probes comprising a "first reporter" is the embodiment where labeled secondary antibodies qualify as the claims "detection probes" (paragraphs [0108]-[0109]). In this sense, Kelso teaches that protein A may be used to coat the particles in order to form arrays of antibody probes (paragraph [0070]).

However, Kelso does not teach attaching the primary antibody attached to the particles (i.e. the "capture probe" of the sandwich immunoassay taught at paragraphs [0108]-[0109]) using biotin/avidin or biotin/streptavidin binding pairs.

Oberhardt was also concerned with attaching antibodies to a solid support (surface). At column 19, lines 38-46, Oberhardt teaches that antibodies can be attached to a solid support by first immobilizing protein A followed by binding of the antibody to protein A. Oberhardt also teaches here that the antibody can be biotinylated and bound to avidin molecules that had been previously coupled.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the protein A method of attaching antibodies to particles taught by Kelso at paragraph [0070] with a method of attaching a biotin to the antibody and avidin to the solid support, since Oberhardt teaches these to be equivalent for the purpose of attaching antibodies to solid supports.

Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelso (US 2003/0129296, filed July 17, 2002, priority date July 17, 2001) in view of Spack et al (US 6,218,132).

The teachings of Kelso have been discussed (see rejection of claims 1, 3-6, 12-14, 16-18, 21, 29-37 and 40 over Kelso under 35 U.S.C. 102(e) above).

This rejection applies to the "masking" alternative recited in claim 1.

With regard to claim 21, upon which claims 22 and 23 depend, Kelso teaches that arrays of different types of capture particles can be formed by attaching different species of capture reagents to different species of encoded particles (see paragraphs [0008] and [0072]; and see paragraph [0006] where "capture particles" are clearly indicated as comprising capture reagents attached to particles). Kelso teaches at paragraph [0055] that "capture particles are encoded such that many unique species of capture particles can be immobilized in the same spot (e.g. allowing the detection of multiple target molecules in a single capture-spot)", and at paragraph [0085]: "capture particle solutions are prepared by pooling subsets of distinctly labeled subpools of capture particles such that the capture particle solution contains many different populations (i.e. unique species) of capture particles. In this regard, multiplex analysis may be carried out." In the context of a sandwich immunoassay as described in paragraphs [0108]-[0109], these teachings imply using different species of capture particles, each species having a different antibody bound thereto (as a "capture probe") for binding different targets ("analytes"), thus meeting the *wherein at least two different analytes are detected by providing...at least two different sets of capture probes* limitations of claim 21. The cited passages also imply *providing at least two different sets of detection probe* (corresponding to the labeled secondary antibodies described in paragraphs [0108]-[0109]).

Kelso does not teach or imply that the two different sets of detection probes (i.e. labeled secondary antibodies; see paragraphs [0108]-[0109]) are labeled with different reporters as recited in claim 22. Note that the limitation "detection oligonucleotides" is not considered required by the claim (see final statement of the rejection under 35 U.S.C. 112, 2nd paragraph above).

Spack teaches a sandwich antibody assay wherein analytes are captured by an immobilized antibody (a "capture probe"), followed by detection using a labeled secondary antibody (a "detection probe"); see figure 1. Moreover, Spack teaches that multiple analytes can be assayed in a multiplex fashion by using two or more detection antibodies, wherein different labels may be chosen in order to distinguish between the analytes (column 11, lines 15-42).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the multiplex antibody sandwich assay implied by the teachings of Kelso by labeling each different secondary antibody with a different label, thus arriving at the invention of claim 22, in order to distinguish between the multiple analytes being detected. It would also have been obvious to use the same label for each antibody molecule of the same species, because, for example, Spack states "a first detection antibody, e.g., an anti-IFN- γ detection antibody, is labeled...with a first detectable label, such as rhodamine, and a second detection antibody, e.g., an anti-IL-10 detection antibody, is labeled with a second detectable label, such as fluorescein". Note Spack did *not* say, "label some anti-IFN- γ detection antibody molecules with rhodamine and some with acridine orange; label some anti-IL-10

detection antibody molecules with fluorescein and some with calcofluor white". Using the same label for all molecules of the same antibody, thus meeting the limitations of claim 23, would have been *prima facie* obvious because using a plurality of different labels for the same antibody would have been (i) unnecessary, (ii) more complicated, (iii) more expensive, (iv) made data analysis more difficult. One of ordinary skill in the art would have been quite cognizant of these issues.

Claims 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelso (US 2003/0129296, filed July 17, 2002, priority date July 17, 2001) in view of Cabib et al (US 5,784,162).

This rejection applies to the "masking" alternative recited in claim 1.

The teachings of Kelso have been discussed (see rejection of claims 1, 3-6, 12-14, 16-18, 21, 29-37 and 40 over Kelso under 35 U.S.C. 102(e) above).

Kelso does not teach that the image recorded at the emission wavelength of the second reporter and the image used for detecting the detection probes were recorded simultaneously. Rather, Kelso recorded the image from the reference fluor of the capture particles first, then recorded the image from the target fluor (see Kelso paragraphs).

Cabib teaches a method of spectral bio-imaging allowing for simultaneous imaging of multiple fluorescent dyes (column 28, lines 37-63):

"The spectral bio-imaging methods of the present invention thus overcome one of the fundamental limitations imposed by filter based approaches to fluorescence imaging. By enabling the simultaneous measurement of the emission spectrum of an unlimited number of fluorescent dyes (including dyes whose emission spectra overlap to a great extent, as demonstrated hereinbelow in the Examples section for the Texas-Red and

Rhodamine fluorophores), spectral bio-imaging eliminates the need for sequentially acquiring images of the emissions of multiple fluorescent probes. The advantage of using a spectral bio-imaging system is greatest when the used fluorescent probes can be excited by a common excitation source. In this case, a single spectral image acquisition can capture the fluorescence emission of an almost unlimited number of dyes and the need to (1) select non-overlapping dyes; (2) change filter cubes; (3) change excitation or emission filters; (4) optimize the focus and/or exposure time or register the images, is eliminated."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Kelso by selecting fluors that could be excited by the same excitation source, and use the method of simultaneous imaging taught by Cabib in order to achieve the numerous advantages recited by Cabib (enumerated in the cited text), thus meeting the limitations of claim 24. In doing so, one would also have inherently met the limitations of claim 25, since Cabib teaches his method avoids the need to register the images (which is essentially what is meant by correcting multiple images so that the images are spatially matched).

Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kelso (US 2003/0129296, filed July 17, 2002, priority date July 17, 2001) in view of Kachab et al (US 2003/0082571, filed April 8, 2002, priority date April 10, 2001).

This rejection applies to the "masking" alternative recited in claim 1.

The teachings of Kelso have been discussed (see rejection of claims 1, 3-6, 12-14, 16-18, 21, 29-37 and 40 over Kelso under 35 U.S.C. 102(e) above).

With regard to claim 37, upon which claim 38 depends, Kelso teaches that arrays of different types of capture particles can be formed by attaching different species of capture reagents ("capture probes") to different species of encoded particles (see paragraphs [0008] and [0072]; and see paragraph [0006] where "capture particles" are

clearly indicated as comprising capture reagents attached to particles). It is also noted that Kelso teaches the use of an affinity interaction to attach capture probes (i.e. antibodies) to the solid supports (i.e. capture particles). Kelso teaches (paragraph [0070]) that "particles coated with protein A may be selected for preparation of an array of antibody probes". This represents an affinity interaction, as protein A binds to antibody through an affinity (not a covalent) interaction.

Kelso does not teach using supports comprising different affinity units with which to attach different capture probes comprising corresponding different cognate affinity units. In other words, Kelso does not teach using different affinity interactions to attach different capture probes to the solid supports. For example, protein A coated particles would all comprise the same affinity unit (protein A), while the various antibodies serving as capture probes would all comprise the same antibody constant region structure recognized by protein A.

Kachab teaches it was known in the art to use affinity interactions such as biotin/avidin (paragraph [0002]) to attach a ligand capable of binding an analyte to a solid support (paragraph [0004]: "these capture systems have been applied in assay platforms whereby one component of the capture system is usually conjugated to a ligand capable of binding specifically to the analyte (anti-analyte) with another component of the capture system being immobilised on a solid support...the binding pair involving immobilization to the solid support has a binding specificity which is irrelevant to or independent of the binding specificity of the analyte/anti-analyte interaction of interest"). Kachab teaches that other such irrelevant binding pairs include

"immunoglobulins and protein A or G" (paragraph [0006]). Kachab teaches at paragraph [0007] (emphasis provided, citations omitted):

"Many different single stage capture systems are available for use as irrelevant binding pairs either for the capture of analytes or analyte/anti-analyte complex species or simply for the immobilisation of anti-analytes or other capture species on a solid support or in a sandwich format of some kind to facilitate detection of the analyte or analyte/anti-analyte complex. It will be appreciated that these capture systems are limited in their applicability as irrelevant binding pairs to systems where multiple analytes, or multi-analyte/anti-analyte complexes or multiple capture species need to be either captured or immobilised on a solid support discretely at specific identifiable capture zones for each of the analytes or analyte/anti-analyte complexes or capture species from a single mixture in solution. In this respect, more than one capture system needs to be used concurrently to achieve the discrete capture needed."

Kachab's solution to this problem was to construct "irrelevant binding pairs" composed of complementary oligonucleotides (paragraph [0008], emphasis provided):

"Complementary nucleic acid binding pairs represent an additional capture system which may be employed as irrelevant binding pairs...Since only nucleic acids having complementary sequences will hybridise with highest specificity and affinity, and since millions of different binding pairs of nucleic acids having sequences and different lengths can be generated...this capture system lends itself well for use in the applications described above...Applications also include multiple analyte or multiple analyte/anti-analyte capture and detection and multiple analyte or capture species (for example antibody) immobilisation on various supports."

Kachab also teaches using his nucleic acid binding pairs to link together species including antibodies and beads (paragraphs [0099]-[0100]).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use numerous different binding pairs of complementary nucleic acid sequences as affinity interactions to immobilize the capture probes (i.e. antibody) to the solid supports (i.e. "capture particles") when practicing the sandwich antibody embodiment of Kelso's method (paragraphs [0108]-[0109]), since Kelso suggested analyzing different analytes in multiplex fashion by attaching different capture probes ("capture reagents") to different solid supports ("capture particles"; paragraphs [0008] and [0072]). Immobilizing multiple different capture reagents to their respective

capture particles in a single reaction, rather than performing a separate immobilization reaction for each different capture reagent/capture particle, would clearly have been more efficient. This would have been a situation where "more than one capture system needs to be used concurrently to achieve the discrete capture needed" as suggested by Kachab.

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kelso (US 2003/0129296, filed July 17, 2002, priority date July 17, 2001) in view of Kolb et al (US 2004/0022777, filed on June 13, 2002, priority date December 15, 1999).

This rejection applies to the "masking" alternative recited in claim 1.

The teachings of Kelso have been discussed (see rejection of claims 1, 3-6, 12-14, 16-18, 21, 29-37 and 40 over Kelso under 35 U.S.C. 102(e) above).

While Kelso generally alludes to screening pharmaceuticals (paragraph [0049]), he does not teach a step of adding a potential or known drug to a cellular sample and analyzing whether the drug induces, inhibits or modulates generation of an analyte.

Kolb teaches a method for screening compounds for the ability to act as antagonists of pro-inflammatory hsp60. The method comprises contacting cells with hsp60 in the presence or absence of the test compound, and then determining whether the test compound has an effect on the production of a pro-inflammatory mediator or effector (see claim 14).

It would have been *prima facie* obvious to one of ordinary skill in the art to apply the method for measuring an analyte as taught by Kelso to the old and well-known drug

screening method taught by Kolb (i.e. adding a test compound to cells and measuring production of an analyte). As a general matter, Kelso teaches a method for quantifying an analyte in a sample; it would have been obvious to use this method, being a known method, for assaying an analyte for any purpose, including the drug screening method of Kolb. For instance, Kelso teaches numerous advantages of his invention over the prior art (paragraphs [0056]-[2258]), including:

"...the solid phases (e.g., capture particles) and coating conditions can be optimized for each different capture reagent.";

"...improves the density, kinetic rate constant, and equilibrium affinity constant of the capture reagent.";

"Nonspecific binding can also be reduced...";

"...increased sensitivity and reduced incubation times."

Claims 2, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelso (US 2003/0129296, filed July 17, 2002, priority date July 17, 2001) in view of Adams et al (WO 90/01564, cited on the IDS of 09/29/2005).

This rejection applies to the "masking" alternative recited in claim 2.

The teachings of Kelso have been discussed (see rejection of claims 1, 3-6, 12-14, 16-18, 21, 29-37 and 40 over Kelso under 35 U.S.C. 102(e) above).

With regard to claim 2, the only distinction over claim 1 is that claim 2 more specifically recites that the detection probes are detection oligonucleotides, and the capture probes are capture oligonucleotides. It is noted that Kelso does teach that the

capture probes (which he refers to as "capture reagents") attached to the solid supports (which he refers to as "capture particles"); see for example figure 13 and paragraph [0006]. However, the only embodiment taught by Kelso which reasonably teaches a detection probe comprising a reporter is the embodiment of a sandwich antibody assay, wherein a labeled secondary antibody can be considered a detection probe comprising a reporter. The labeled nucleotide shown in figure 13, which is incorporated into the oligonucleotide capture probe, cannot be said to be "capable of binding to the analyte" (i.e. the target nucleic acid hybridized to the immobilized primer in figure 13), since the nucleotide itself would not bind thereto.

Therefore, Kelso does not teach a method as recited in claim 2 involving *oligonucleotides*. Nevertheless, Kelso does teach that "[a]ny method for detecting target molecules that, for example, employs a solid support, or may be adapted to employ a solid support, may be performed with the film-immobilized capture particles of the present invention" (paragraph [0108]).

Adams teaches detection of nucleic acid targets by a method comprising *providing detection oligonucleotides being labeled with a first reporter* (figure 1, probes 4-6), *which oligonucleotides are capable of binding to the analyte* (figure 1, RNA A-C, and page 20, line 21 through page 22, line 17);

providing a solid support (figure 1, probes 1-3 can be seen immobilized on a solid support);

providing capture oligonucleotides (figure 1, probes 1-3) being bound to the solid support, which capture oligonucleotides are capable of binding to the analyte, thus concentrating the analyte on the solid support;

contacting the sample with the detection oligonucleotides, the solid support, and the capture oligonucleotides (figure 1, the rRNA A-C constitute a sample comprising these target analytes; it can be clearly seen that these analytes are in contact with both the capture oligonucleotides on the solid support, and the detection oligonucleotides).

With regard to claim 19, Adams teaches regarding the labeled probes (see figure 1), which correspond to the claimed "detection oligonucleotides", that, generally, a ligand molecule is covalently bound to the probe. The ligand then binds to an anti-ligand molecule which is either inherently detectable or covalently bound to a, for example, a fluorescent compound (see page 16, lines 30-36).

With regard to claim 20, both Kelso (paragraph [0031]) and Adams (page 4, lines 12-13) teach attaching the capture probe to the solid support via a linker (spacer).

Thus, Adams taught a binding assay for detecting nucleic acid analytes, and it would have been *prima facie* to one of ordinary skill in the art at the time the invention was made to carry out the method of Adams using the more modern approach taught by Kelso, by affixing the capture oligonucleotides to capture particles and conducting the binding assay and detection according to the teachings of Kelso. By doing so, one would have arrived at the claimed invention since Kelso teaches the limitations regarding detection by taking an image of the "second reporter" of the solid support, creating a mask, and using the mask to analyze an image of the "first reporter" of the

capture oligonucleotides. One would have been motivated to do so because Kelso expressly endorses using his improved methods for any method for detecting target molecules that involves a solid support. Kelso also points out several advantages to his method in paragraphs [0056]-[2258], including:

"...the solid phases (e.g., capture particles) and coating conditions can be optimized for each different capture reagent.";

"...improves the density, kinetic rate constant, and equilibrium affinity constant of the capture reagent.";

"Nonspecific binding can also be reduced...";

"...increased sensitivity and reduced incubation times."

Hence, one would have clearly seen Kelso's methods of binding assays and imaging as more improved over the method of Adams, and would therefore have been motivated to adapt Adams' "sandwich oligonucleotide" assay format to Kelso's more modern techniques.

Claims 1, 2, 7-9 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al (WO 90/01564, cited on the IDS of 09/29/2005) in view of Li et al (Nucleic Acids Research, Vol. 30, No. 2 e5, January 15, 2002, pp 1-9), and as evidenced by Yamamoto (US 2008/0213762).

This rejection applies to the "quenching" alternative recited in claims 1 and 2.

With regard to claims 1 and 2, Adams teaches detection of nucleic acid targets by a method comprising *providing detection oligonucleotides being labeled with a first*

reporter (figure 1, probes 4-6), which oligonucleotides are capable of binding to the analyte (figure 1, RNA A-C, and page 20, line 21 through page 22, line 17);

providing a solid support (figure 1, probes 1-3 can be seen immobilized on a solid support);

providing capture oligonucleotides (figure 1, probes 1-3) being bound to the solid support, which capture oligonucleotides are capable of binding to the analyte, thus concentrating the analyte on the solid support;

contacting the sample with the detection oligonucleotides, the solid support, and the capture oligonucleotides (figure 1, the rRNA A-C constitute a sample comprising these target analytes; it can be clearly seen that these analytes are in contact with both the capture oligonucleotides on the solid support, and the detection oligonucleotides).

Adams does not teach that the detection is conducted in the presence of quenching probes binding to surplus detection probes not being bound to the analyte and thereby quenching at least partially an emission of the first reporter of said surplus detection probes, as recited in claims 1 and 2. Consequently, Adams does not teach the limitations of claims 7-9, 26 and 27.

With regard to claims 1 and 2, Li teaches double-stranded probe complexes comprised of a longer oligonucleotide (detection oligonucleotide) complementary to a target (analyte) and labeled with a fluorophore (first reporter), and a shorter oligonucleotide (quenching oligonucleotide) labeled with a quencher (see figure 2). The probe complex is designed such that in the absence of a target, the two strands of the complex remain associated with one another, quenching the fluorescence of the

fluorophore (see figure 2 and page 3, "Design and preparation of double-stranded probes"). However, in the presence of a target, the longer duplex formed by the detection oligonucleotide and target is thermodynamically favored over the shorter duplex formed by the detection oligonucleotide and quenching oligonucleotide (see figure 2 and page 2, "Reaction kinetics with double-stranded probes"). Hence, Li's probes are designed to be used such that detection occurs in the presence of quenching probes binding to surplus detection probes not being bound to the analyte and thereby quenching at least partially an emission of the first reporter of said surplus detection probes, as recited in claims 1 and 2.

With regard to claim 7, since the hybrid formed by the labeled strand (i.e. the detection oligonucleotide) of Li's probe complex with the target is longer (i.e. comprises more base-paired nucleotides) than is the hybrid formed by the labeled and quencher strands of the probe complex, the former *inherently* has a higher melting temperature than the latter.

With regard to claim 8, Li teaches that the reaction rate was maximal when the labeled strand of the probe exceeded the quencher strand by 7 nt (see page 2, "Reaction kinetics with double-stranded probes"). The probe having a 7 nt difference between the longer and shorter strands is shown in figure 1A, middle panel of the bottom row. In the hybridized probe complex, base pairing occurs between the sequence AGCAACCTCAAACAGAC of the longer strand and the complementary sequence of the shorter strand. This hybrid has a T_m of 45°C as calculated by the algorithm at <http://www.pitt.edu/~rsup/OligoCalc.html>:

Oligo Calculator

Enter Oligo Sequence in Box	
<div>AGCAACCTCAAACAGAC</div>	
Length <input type="text" value="17"/>	Melting Temperature (T _m) <input type="text" value="45"/> °C
<input type="text" value="47"/> %GC content	Molecular Weight: <input type="text" value="5140"/> daltons (g/M)
<input type="button" value="Calculate"/>	OD of 1 is equal to <input type="text" value="5020"/> nanoMolar.

In the hybrid formed between the longer strand of the probe complex and the target, base pairing would occur between the whole length of the longer probe strand and complementary sequence in the target (i.e. over the sequence AGCAACCTCAAACAGACACCATGG). This hybrid would have a T_m of 57°C, which is at least 10°C higher.

With regard to claim 9, since the whole purpose of Li's probe was to allow for hybridization of between the labeled strand of the probe complex to the target (see figure 2), it would have been obvious to perform this hybridization under conditions allowing the hybridization to occur.

With regard to claim 26, Li's shorter probe strand comprised a quenching unit (see figure 2).

With regard to claim 27, in Li's probe complexes, the "first reporter" on the longer probe strand ("detection oligonucleotide") and the quencher on the shorter strand

constitute a FRET donor-acceptor pair (e.g. see figure 5: Li teaches FAM/dabcyl, HEX/dabcyl and TAMRA/dabcyl, each of which represents a FRET pair).

With regard to claim 28, as evidenced by Yamamoto (paragraphs [0050], [0097], [0100]), dabcyl is a dark quencher.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the simple linear detection probes used by Adams with the double-stranded probes taught by Li, since Li teaches that his probes have enhanced specificity (see abstract: "comparison of double-stranded probes with corresponding linear probes confirms that the presence of the complementary strand significantly enhances their specificity").

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Cai et al (US 7,202,036)

Nolan et al (Anal. Chem. 75:6236-6243, November 15, 2003)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Samuel Woolwine/
Examiner, Art Unit 1637